ANNALS OF SURGERY
Vol. 229, No. 5, 684–692

Prospective, Randomized Comparison of Epidural *Versus* Parenteral Opioid Analgesia in Thoracic Trauma

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Objective

To evaluate systemic *versus* epidural opioid administration for analgesia in patients sustaining thoracic trauma.

Summary Background Data

The authors have previously shown that epidural analgesia significantly reduces the pain associated with significant chest wall injury. Recent studies report that epidural analgesia is associated with a lower catecholamine and cytokine response in patients undergoing elective thoracotomy compared with patient-controlled analgesia (PCA). This study compares the effect of epidural analgesia and PCA on pain relief, pulmonary function, cathechol release, and immune response in patients sustaining significant thoracic trauma.

Methods

Patients (ages 18 to 60 years) sustaining thoracic injury were prospectively randomized to receive epidural analgesia or PCA during an 18-month period. Levels of serum interleukin (IL)-1β, IL-2, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α) were measured every 12 hours for 3 days by enzyme-linked immunosorbent assay. Urinary catecholamine levels were measured every 24 hours. Independent observers assessed pulmonary function using standard techniques and analgesia using a verbal rating score.

Results

Twenty-four patients of the 34 enrolled completed the study. Age, injury severity score, thoracic abbreviated injury score, and length of hospital stay did not differ between the two groups. There was no significant difference in plasma levels of IL-1β, IL-2, IL-6, or TNF-α or urinary catecholamines between the two groups at any time point. Epidural analgesia was associated with significantly reduced plasma levels of IL-8 at days 2 and 3, verbal rating score of pain on days 1 and 3, and maximal inspiratory force and tidal volume on day 3 *versus* PCA.

Conclusions

Epidural analgesia significantly reduced pain with chest wall excursion compared with PCA. The route of analgesia did not affect the catecholamine response. However, serum levels of IL-8, a proinflammatory chemoattractant that has been implicated in acute lung injury, were significantly reduced in patients receiving epidural analgesia on days 2 and 3. This may have important clinical implications because lower levels of IL-8 may reduce infectious or inflammatory complications in the trauma patient. Also, tidal volume and maximal inspiratory force were improved with epidural analgesia by day 3. These results demonstrate that epidural analgesia is superior to PCA in providing analgesia, improving pulmonary function, and modifying the immune response in patients with severe chest injury.

Thoracic trauma is a significant cause of morbidity and mortality in our society. It ranks second only to head injury as a cause of traumatic death in the United States. One of every four deaths resulting from trauma is attributable to a thoracic etiology.[1] Pain associated with flail chest or multiple rib fractures can result in voluntary splinting and muscle spasms, which subsequently leads to decreased ventilation and atelectasis. Compromise of pulmonary function can also cause hypoxemia, an increase in shunt fraction, or pneumonia, which may require mechanical ventilation.[2] Adequate relief of rib and chest-wall pain allows the patient to breathe deeply, avoid intubation,[3] and clear secretions

Presented at the 110th Annual Meeting of the Southern Surgical Association, December 6–9, 1998, The Breakers, West Palm Beach, Florida.
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Accepted for publication December 1998.

Table 1. PROPOSED ROLES OF CYTOKINES IN RESPONSE TO INJURY

Cytokine	Presumed Function
TNFα	Early proinflammatory cytokine; may release other cytokines (proteolysis largely steroid-mediated)
IL-1	Proinflammatory cytokine
IL-2	Potentially antiinflammatory; stimulates T lymphocytes
IL-6 (hepatocyte-stimulating factor)	Stimulates acute-phase hepatic protein synthesis
IL-8 (neutrophil-activating peptide-1)	Neutrophil and lymphocyte chemoattractant and activator Implicated in acute lung injury

effectively, minimizing pulmonary complications.[4] We have previously shown that the epidural route of analgesia is superior to intrapleural administration for analgesia and improves pulmonary function in patients with thoracic trauma.[5]

Any acute injury produces a spectrum of physiologic responses. The neuroendocrine system responds by increased activity, which includes autonomic control of cardiac contractility and peripheral vascular tone, hormonal response to stress and volume depletion, and local microcirculatory mechanisms that are organ-specific and regulate regional blood flow. Multiple stimuli associated with traumatic injury can initiate these responses, including pain, hypoxemia, hypercarbia, and emotional arousal, to name a few.[6,7] Somatic pain is generated by the response of nociceptors through the A-delta fibers, which are activated by high-intensity stimuli. These afferent signals then undergo central integration that modulates the efferent output, leading to sympathetically mediated vasoconstriction and secretion of corticotropin-releasing factor, the primary autonomic and endocrine responses to somatic pain, respectively. Repeated insults or hemorrhage potentiate this effect. Blocking afferent signals resulting from pain in patients undergoing elective thoracotomy has been shown to reduce systemic catecholamine levels significantly.[8]

An additional host response to injury involves a coordinated expression of cytokines that act both systemically and locally with profound effects on organ function. Cytokines differ from the classic hormones in the following manner:

1. They are bioactive at very low concentrations locally that may not be detectable systemically.
2. They are produced by many cell types at many sites in the body.
3. They are induced based on the nature of the insult.
4. They have important autocrine, paracrine, and endocrine functions (Table 1).
5. Serum levels of cytokines probably represent largely overflow rather than an endocrine function.[9]

A traumatic wound, with or without hypotension, produces similar systemic immunomodulation. Levels of tumor necrosis factor-alpha (TNF-α) may increase after injury.[10] Serum levels of interleukin (IL)-1β are elevated,[11] IL-2 levels are decreased,[12,13] and IL-6 levels are elevated shortly after injury and remain elevated for several days.[14] Finally, within 8 hours of injury, circulating levels of IL-8 are increased.[15]

Although many studies have characterized the inflammatory mediators associated with traumatic injury,[11–13] little is know about the effects of the route of analgesia administration on pain relief, pulmonary function, and systemic inflammatory mediators in patients with significant thoracic injury. Randomized controlled studies of patients undergoing elective thoracotomy have proven that epidural anesthesia and postoperative continuous epidural analgesia decrease the stress response associated with surgical trauma compared with parenteral analgesia.[8] However, in that study, epidural anesthesia was given before surgery, before the stress was initiated.

The purpose of this study was to investigate the effect of route of analgesia delivery after severe chest injury on analgesia, pulmonary function, urinary catecholamine levels, and plasma cytokine levels by comparing parenteral *versus* epidural opioid analgesia. Effective pain control should improve pulmonary mechanics and reduce the neuroendocrine and immune response. Any of these outcomes may also reduce complications.

MATERIALS AND METHODS

Patient Selection

This study was conducted with the approval of the Institutional Review Board at the University of Cincinnati College of Medicine. All patients (ages 18 to 60 years) arriving at the Center for Emergency Care at University Hospital from Sept. 1, 1996, through March 1, 1998, with thoracic trauma were evaluated for study eligibility. Significant thoracic trauma for study enrollment was defined as one or more of the following:

1. Three or more consecutive rib fractures
2. A flail chest wall segment
3. Pulmonary contusion (diagnosed by mechanism of injury, arterial blood gases, and chest radiograph or noted on thoracic computed tomography)
4. Sternal fracture.

Exclusion criteria included contraindications to epidural catheter placement (coagulopathy, infection at insertion site,

sepsis, or hypovolemic shock), morbid obesity (100 lb more than ideal body weight), evidence of spinal cord injury above T10, Glasgow Coma Score $<$ 15, adrenal insufficiency, use of steroids within 6 months before injury, need for vasoactive agents to support blood pressure, immunodeficiency disease, pregnancy, inability to communicate effectively, or history of allergy to local anesthetics or opioids. All study subjects were enrolled within 24 hours of admission after informed consent was obtained. Using computer-generated numbers, patients were randomized using a restricted scheme to receive opioid delivered by self-administered patient-controlled analgesia (PCA) or thoracic epidural catheter.

Patient demographic data included age, gender, injury severity score (ISS),[16] thoracic abbreviated injury score (thoracic AIS),[17] and length of stay (intensive care unit, ward, and entire hospital admission).

Patient-Controlled Analgesia

All patients were assessed by anesthesiologists from the acute pain service. Patients randomized to patient-controlled analgesia (PCA) received a loading dose of intravenous morphine 0.1 mg/kg before establishment of PCA. The infusion was titrated by a member of the acute pain service to maximize pain relief before handing over the control of the system to the patient. The PCA regimen used morphine (1 mg/ml) in bolus doses of 2 mg with a lock-out duration of 10 minutes. There was no background infusion. All patients were instructed regarding use of the PCA system. Additional doses were given if deemed necessary only by a member of the acute pain service.

Epidural Catheter Placement

Thoracic epidural catheters were placed by an anesthesiologist (Tuohy catheter, Perifex Custom Epidural Anesthesia Tray, B. Braun Medical Inc., Bethlehem, PA) in the epidural space between T5 and T7. A 3-ml test dose of lidocaine 1.5% with epinephrine 1:200,000 (Astra Pharmaceutical Products, Westborough, MA) was then administered through the epidural catheter to exclude subarachnoid or intravascular location of the catheter. Sensory testing of appropriate thoracic dermatomes was performed 10 minutes after administering this dose to confirm epidural placement of the catheter. After a successful test dose, the catheter was further dosed with an injection of fentanyl (50 μg) and 3 mg preservative-free morphine (Duramorph, Elkins-Sinn, Cherry Hill, NJ). Within 1 hour after placement of the catheter, a continuous infusion of bupivacaine 0.25% (Astra) and morphine (0.005%) was initiated at a rate of 4 to 6 ml/hr using an infusion pump (Abbott, Chicago, IL). Drugs for epidural use were prepared by the central pharmacy in a sterile environment and were free of any preservatives. A member of the acute pain service adjusted the infusion rates to optimize pain relief and minimize side effects.

Pain relief was assessed for both groups using a standard verbal rating scale (0, no pain to 10, the worst imaginable pain). Dynamic pain scoring (*i.e.*, at rest, on deep inspiration, and on movement) was performed at each time point. During the first hour, the verbal rating score was assessed by one of the authors (JC or GS); subsequently it was assessed by nursing staff trained in pain-assessment techniques. Verbal rating score assessments were then made every 12 hours.

Blood Sample Collection

Blood was collected from patients by venipuncture, from central venous access, or from arterial access on admission and daily for the duration of the study. Approximately 30 ml of blood was collected at each time point in a sterile glass tube. It was immediately centrifuged at 2000 rpm for 10 minutes and stored at -80°C until cytokine assays were performed.

Cytokine Measurements

All cytokine measurements were performed with a commercially available enzyme-linked immunosorbent assay kit (Endogen, Woburn, MA) for the quantitative measurements of IL-1β, IL-2, IL-6, IL-8, and TNF-α. Individual procedures were performed in accordance with the methods described by the manufacturers. Briefly, plasma samples from the patients were loaded into 96-well polystyrene microtiter plates that were precoated with a monoclonal antibody directed against the target cytokine. Biotinylated antibody reagent was added to each well of the precoated plate and incubated at room temperature for 1 to 2 hours. Samples were washed three times with buffer solution between each step. Streptavidin-HRP was then added to each well and incubated at room temperature for 30 to 60 minutes. Premixed TMB substrate solution was then added to each well and incubated at room temperature in the dark for 30 to 60 minutes. The reaction was then terminated with stop solution, and optical density was measured at an absorbance of 450 nm.

Catecholamine Measurements

Patients were not allowed to consume caffeinated coffee, soft drinks, or chocolate during the study period to avoid false elevation of catecholamine levels. Similarly, the following medications known to increase catecholamine concentration were not allowed before or during the study: chlorpromazine, monoamine oxidase inhibitors, methyldopa, nitroglycerin, perphenazine, phenothiazines, promethazine, quinidine, dopamine, and quinine. Twenty-four-hour urine samples were collected in a 3-L container on ice with 25 ml of 6N hydrochloric acid added as a preservative, and refrigerated. Total volumes were accurately recorded using a graduated cylinder. Within 48 hours of completion of daily collections, two 100-ml aliquots were frozen at

Table 2. PATIENT DEMOGRAPHICS

Route of Analgesia	No. of Patients	Male/Female	Age	ISS	AIS	LOS	ICU LOS	Ward LOS
Epidural	13	8/5	37	26.6	3.7	11	3.8	6.6
PCA	11	6/5	40	23.4	3.7	9.7	4.1	4.7

There was no significant difference between the two study populations in terms of clinical characteristics.
ISS, Injury Severity Score; AIS, thoracic abbreviated injury score; LOS, length of hospital stay; ICU, intensive care unit.

−10°C. At the completion of the 72-hour collection period, epinephrine and norepinephrine concentrations were determined by high-pressure liquid chromatography (Quest Diagnostics, Teterboro, NJ).

Pulmonary Parameters

Daily measurements of pulmonary mechanics were performed, and the respiratory therapist recorded supplemental oxygen requirements. Determination of maximal inspiratory force (MIF) was made using an aneroid manometer (Puritan-Bennett Corp., Carlsbad, CA) connected to a valved T piece that permitted expiration.[18] A Boehringer respirometer (Boehringer Laboratories Inc, Wynnewood, PA) was used to measure tidal volume (V_T). Forced expiratory volume at 1 second was also recorded.

Statistics

Differences in continuous variables (*e.g.*, cytokines, catecholamines, age) were determined by Student's t tests. Score-type data (ISS, verbal rating score) were analyzed using the nonparametric Wilcoxon test. A probability value < 0.05 was regarded as significant.

RESULTS

Patient Population

Thirty-four patients were initially enrolled in the study. Data from 10 patients could not be analyzed for one or more of the following reasons: inability to complete the study, voluntary withdrawal, or conflict with exclusion criteria. Twenty-four patients completed the study. Thirteen received epidural analgesia and 11 PCA (Table 2). The two groups did not differ in terms of age, gender, ISS, thoracic AIS, or hospital, intensive care unit, or floor length of stay.

Patient Analgesia

During the first 24 hours of study, the epidural group had a significant ($p < 0.05$) reduction in pain score with coughing compared with patients receiving PCA (Fig. 1). After 48 hours, there was no difference in pain scores between the two routes of opioid administration. On day 3, the epidural group had a 38.7% reduction in pain score compared with the PCA group, whose score was approximately 6.2, the same as for day 2. The epidural group's pain score on day 3 (3.8) was significantly lower ($p < 0.05$) than that of the PCA group.

Respiratory Function

Supplemental oxygen requirements and forced expiratory volume were not altered by the route of opioid administration (data not shown). In contrast, patients receiving PCA had a gradual decline (15%) in MIF throughout the study period, whereas the epidural group had a continual increase (23%). By day 3, the epidural group had a significant ($p < 0.05$) increase in MIF *versus* the PCA group (Fig. 2). V_T measurements showed a similar but more dramatic difference between the groups. Although the V_T for the PCA group on day 1 was greater than that of the epidural group (587 cc *vs.* 406 cc), the difference did not reach significance. However, throughout the study period, V_T for the PCA group continually fell: by day 3 it was 327 cc (56% of day 1). In contrast, the epidural group had a continual improvement (45% increase from day 1) in V_T: by day 3, V_T was

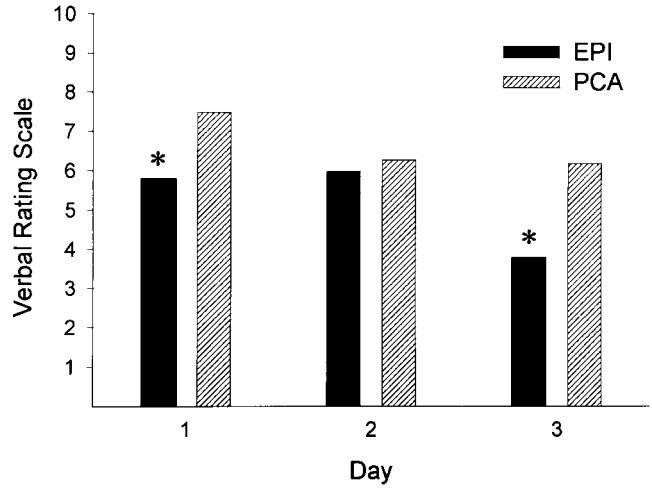

Figure 1. Effect of route of opioid administration on patient verbal rating score with coughing. The epidural route was significantly ($p < 0.05$) better for providing pain relief than the intravenous route on days 1 and 3.

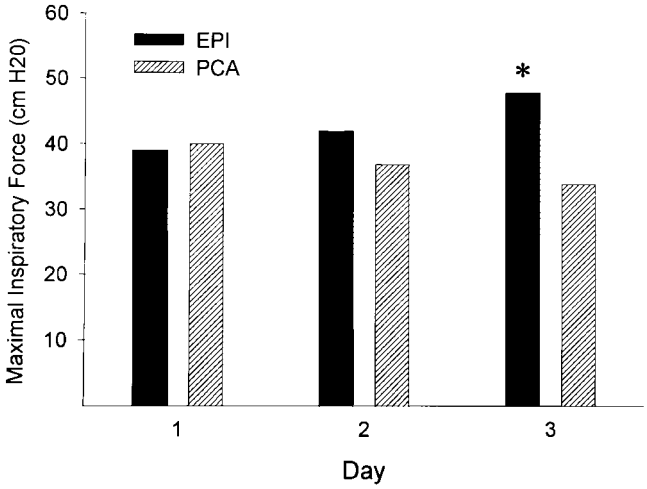

Figure 2. Maximal inspiratory force measurements increased for the patients receiving epidural analgesia throughout the study period. In contrast, the PCA group had a progressive decline in maximal inspiratory force ($p < 0.05$).

significantly ($p < 0.05$) greater in the epidural group than in the PCA group (590 cc *vs.* 327 cc) (Fig. 3).

Plasma Cytokines

IL-1β, IL-2, and TNF-α were detectable at all time points in both groups, but levels were consistently low and demonstrated no fluctuation throughout the study. There was no significant difference in plasma levels of these cytokines throughout the study period (Fig. 4).

In contrast, plasma levels of IL-6 were elevated at all time points throughout the study in both groups (Fig. 5). Although a reduction in plasma IL-6 levels was demonstrated in the epidural group, no significant difference was detected between the two groups because of variability problems.

Plasma levels of IL-8 were detectable at all time points in the study for both groups. In contrast to IL-6, plasma levels of IL-8 were significantly lower in the epidural group (5.8 and 5.7 pg/ml) *versus* the PCA group (11.5 and 13.0 pg/ml) by days 2 and 3, respectively (Fig. 6).

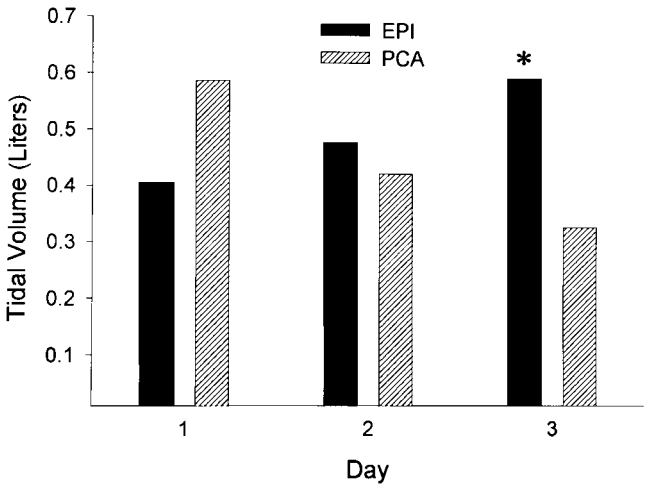

Figure 3. Tidal volume measurements increased in the epidural group and decreased in the PCA group throughout the study ($p < 0.05$).

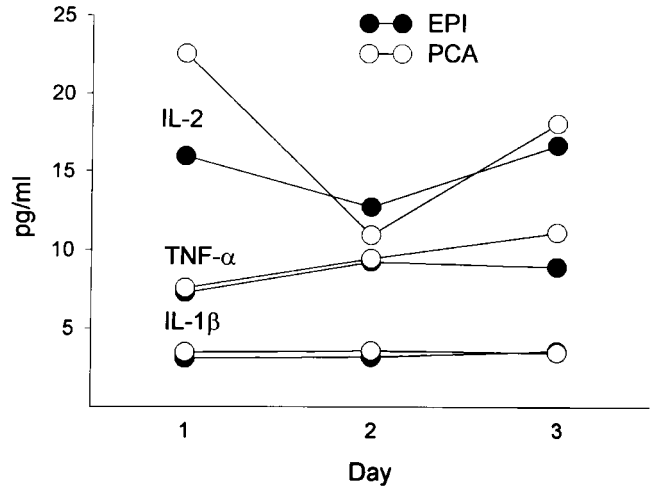

Figure 4. Plasma levels of IL-1β, IL-2 and TNF-α were not altered by the route of analgesic administration.

Urinary Catecholamines

Twenty-four-hour urinary catecholamines were collected and quantified because of the large variation in serum and plasma levels associated with acute injury. Both norepinephrine and epinephrine demonstrated reduced trends over the 3-day period of collection (Fig. 7). However, there was no significant difference with either catecholamine between the two groups.

DISCUSSION

Thoracic injury continues to be a significant cause of death and complications in the trauma population. A major

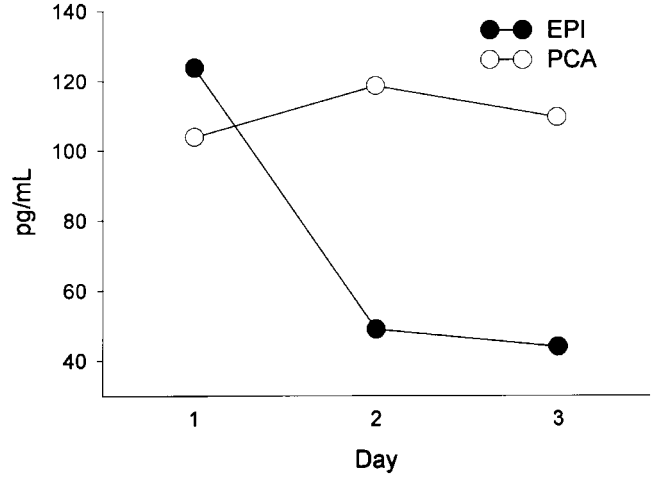

Figure 5. Plasma levels of IL-6 were elevated at all time points. By days 2 and 3, the measurements were markedly lower in the epidural group. However, this was not statistically significant.

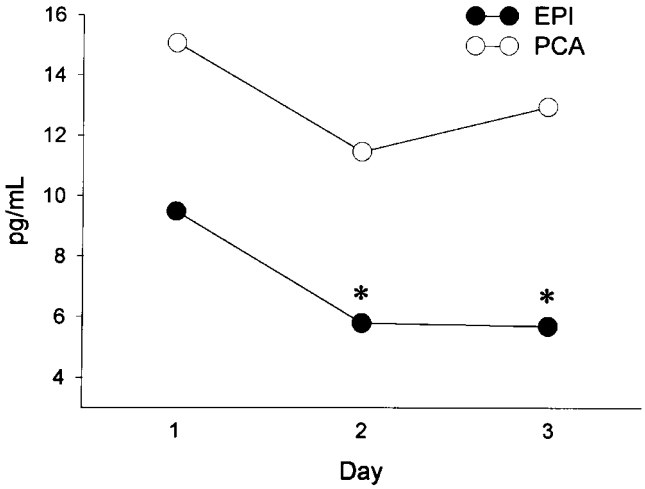

Figure 6. Epidural administration of opioid significantly lowered plasma levels of IL-8 throughout the study, reaching statistical significance on days 2 and 3 ($p < 0.05$).

part can be attributed directly to impaired pulmonary mechanics secondary to the pain associated with chest-wall injury. Therefore, adequate control of chest-wall pain is imperative in the management of these injuries, because splinting and atelectasis can lead to pulmonary complications. Epidural analgesia was associated with a lower verbal rating score of pain on days 1 and 3, suggesting that it provides better pain relief for chest injury than PCA. These findings were associated with a larger V_T and MIF by day 3, indicating that the reduced pain allowed improved ventilatory mechanics. This could have important clinical implications, because persistent chest-wall pain can lead to atelectasis and pneumonia.

Traumatic injury can also trigger the neurohormonal response, causing the release of catecholamines and a cascade of inflammatory cytokines. Recent studies have demonstrated that epidural analgesia is associated with lower catecholamine release after elective thoracic surgery.[8] However, in that study, epidural analgesia began before the injury (incision).

Catecholamines are biologically active amines derived from the amino acid tyrosine and are typically stored in chromaffin granules within sympathetic nerve terminals and in the cells of the adrenal medulla.[19] Secretion of epinephrine and norepinephrine occurs in response to a variety of stressful stimuli, including pain, hemorrhage, surgery, and anoxia. Because of the wide distribution of adrenergic receptors, effects achieved by catecholamines are both varied and rapid, and often include marked effects on the nervous and cardiovascular systems, metabolic rate, temperature, and smooth muscle. Although the effects of catecholamines tend to be shortlived secondary to a short plasma half-life, persistent secretion can prove detrimental to several organ systems. Recent studies have demonstrated decreased levels of circulating catecholamines in patients receiving epidural analgesia after elective thoracotomy.[8] Excessive catecholamine secretion in response to severe thoracic injury, therefore, could potentially be blunted by analgesic delivery into the epidural space. In the current study, urinary catecholamines were elevated at all time points, but the route of analgesic administration did not alter levels. Although the groups were matched evenly in ISS and thoracic AIS, this lack of difference could reflect differences in nonthoracic injuries between the two groups. Also, although attempts were made to preserve urine samples on iced hydrochloric acid over the 24-hour periods, catecholamine degradation may have varied. Lack of a consistent, uniform cooling technique may have affected urinary catecholamine levels.

The finding that plasma levels of IL-1β, IL-2 and TNF-α were not significantly different between the two groups is not surprising. Although numerous studies have shown increased levels of the inflammatory cytokines IL-1β and TNF-α, as well as elevated levels of the potentially antiinflammatory cytokine IL-2 under certain stressful conditions, recent studies seem to indicate that detection of these mediators may not be reliably reproducible. Recent studies have suggested that cytokine soluble receptors may provide a more accurate marker of systemic cytokine release, because these receptors are typically shed into the circulation and have a longer half-life than their counterparts.

Formerly known as hepatocyte-stimulating factor, IL-6 is most commonly associated with regulation of hepatic acute-phase protein synthesis and has recently been associated with traumatic injury, systemic inflammation, and sepsis.[19] Several studies have correlated elevated levels of IL-6 with multiple organ failure and increased death rates in patients with severe trauma.[20,21] In our study, both groups had increased IL-6 levels. Although there was no significant difference in plasma IL-6 levels between the two groups, a reduced trend was noted in patients receiving epidural analgesia. This lack of significance could be secondary to large standard deviations

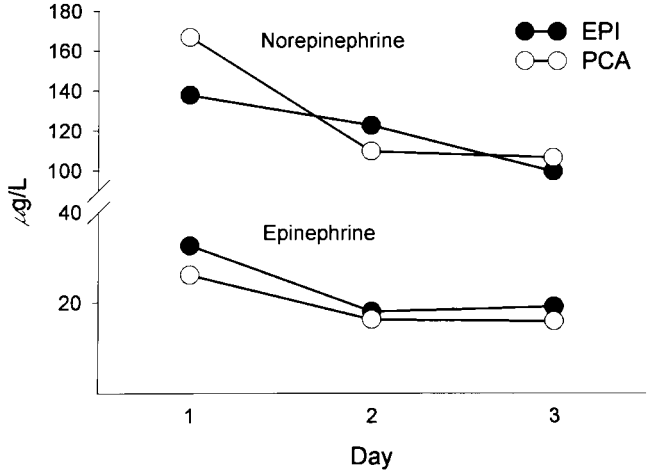

Figure 7. There was no difference in the 24-hour urinary catecholamine metabolite concentration between the study groups.

noted in this group and would potentially gain power with a larger sample size. Nevertheless, increased levels of the inflammatory cytokine IL-6 may not necessarily incite inflammatory events and may in fact be a marker for acute or chronic inflammation.

IL-8, also known as neutrophil-activating peptide 1, is a member of the chemokine family that functions as a neutrophil and lymphocyte chemoattractant and activator.[22] It is produced by a variety of cell types, including macrophages, endothelial cells, fibroblasts, and lymphocytes,[23] and can be expressed by a variety of inflammatory stimuli. The effects of IL-8 on neutrophils include upregulation of adhesion molecules, promotion of transendothelial migration, and stimulation of degranulation, with subsequent respiratory burst.[24] Numerous studies have shown increased systemic levels of IL-8 after trauma and a positive correlation with ISS and multiple organ failure.[20,25] Recent studies have also demonstrated that IL-8 is elevated both systemically and in bronchiolar alveolar lavage fluid from patients with acute respiratory distress syndrome,[26,27] and some have suggested it may be implicated in the pathogenesis of acute respiratory distress syndrome. It is therefore interesting that in the current study, plasma levels of IL-8 were significantly lower in patients receiving epidural analgesia by days 2 and 3. Because the studies reported implicate IL-8 in the pathogenesis of postinjury organ dysfunction,[20,25–27] reduced levels of systemic IL-8 could potentially lower the incidence of complications.

Results of the current study should be interpreted cautiously for several reasons. First, the biologic activity of the cytokines studied was not assessed, and the cytokines detected may simply play a role as a marker of inflammation, not as potential inflammatory inciters or effectors. Second, the source of cytokines in the plasma was not determined and could reflect either paracrine or autocrine secretion from a number of different sources. Third, fluctuations in plasma cytokines may not reflect the true quantity, because all cytokines tested have short half-lives. Measurement of plasma or serum soluble receptors may prove to be a more accurate reflection.

Finally, although the results did show significant differences and trends in the proteins assayed, as well as in the pulmonary function and pain relief, the anticipated number of patients completing the study was not achieved. A larger sample size might show more significant differences, particularly in lower plasma IL-6 levels, shorter hospital stay, fewer complications, and a lower overall cost in patients with severe thoracic injury treated with epidural analgesia. Further studies are needed to define the role of epidural analgesia in severe thoracic injury.

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Discussion

DR. BASIL A. PRUITT, JR. (San Antonio, Texas): I congratulate Dr. Fischer, Dr. Moon, and their colleagues on this very practical study extending their earlier observation that epidural analgesia provides better pain control in patients with chest wall injury than does patient-controlled analgesia. The present study indicates that that improved pain control is associated with an increase in maximal inspiratory force, in tidal volume, and reduction in plasma levels of IL-8.

To evaluate the importance of these observations, we need some outcome information. Since both IL-6 and IL-8 are endogenous pyrogens, were body temperatures of the EPI—that's the epidural analgesia patients—lower on the average than that of the PCA patients?

In light of the improved pulmonary mechanics, was the duration of intubation or mechanical ventilation in the epidural analgesic group shorter than in the PCA group?

Additionally, with improvement in pulmonary function, why were total length of stay and ward length of stay longer in the EPI group? Although there was no significant difference in those differences, I wonder if you think that was just a Type II error because of the small number in each of the study groups.

Lastly, even though you propose that lower IL-8 levels are good, others have related such a change to an increased risk to infection. In that vein, did the epidural analgesia patients with lower plasma levels of IL-8 have a greater incidence of pneumonia or bronchitis?

Do you propose, on the basis of these studies, to evaluate the effect of anti–IL-8 agents in your next 35 ICU patients, or possibly employ an anti–IL-8 receptor antibody which would inhibit IL-8–induced neutrophil chemotaxis?

DR. C. JAMES CARRICO (Dallas, Texas): The relatively small number of patients, 34 patients in 18 months, I don't think requires any apology. It's a very difficult population. And as was pointed out, the total available in that period of time was 44 patients.

In the manuscript, the statement is a little stronger than the verbal presentation. The authors state that epidural analgesia was superior to patient PCA in providing analgesia, improving pulmonary function, and reducing the immune response. The first two points are absolutely valid. Analgesia was demonstrably improved, pulmonary function was measurably enhanced by the third day. The reduction in the immune response might better be described as modification of the immune response. The only thing which was clearly demonstrated statistically was a reduced plasma level of IL-8.

Again, the question there is was this a cause and effect? Clearly, you demonstrated an association between the use of epidural analgesia and a decreased plasma level of IL-8. The question is, can you provide us any information or assurance that this was cause and effect rather than simply a marker of the inflammatory response or, as Dr. Pruitt suggested, a reflection of subclinical infection in the patients who had the less improved lung volume?

I also echo Dr. Pruitt's question about whether reduction of IL-8 is beneficial or detrimental. IL-8 has been associated with increased incidence of multiple organ failure and systemic inflammatory response, but as a PMH chemoattractant, it should be an important host defense against infection. So can you tell us anything about the difference in infections in those groups of patients? Admittedly, the numbers were small.

Last but not least, can you give us some idea about how applicable this approach is? I think your total population was 44 patients. Ten were eliminated because of study exclusions. How many of those were study exclusions, how many of those were practical exclusions so you could not have used the therapy? Then you had ten other patients where you couldn't complete the study. How many of those were dropped because of complications of the epidural analgesia? So the real question is, clearly you have demonstrated physiologic effect. How frequently are we going to be able to use this in patients with blunt thoracic trauma?

DR. R. NEAL GARRISON (Louisville, Kentucky): (This study) is provocative, but, due to the small numbers in each comparative group, not definitive in recognizing a clear benefit for epidural *versus* parenteral pain management. But I suspect that further patients studied will translate into better clinical outcomes when the epidural anesthetic technique is utilized.

At the risk of duplicating Dr. Pruitt and Dr. Carrico, I would like to point out that in your paper, clinical findings were not listed for either group as concerns complications during the hospitalization. What complications did occur, if any, and was there any hint at a decrease in outcome complications during hospitalization?

Were there any patients where the epidural catheter was misplaced or malfunctioned?

Were the total amount of drugs administered comparable? I suspect that there was some systemic absorption of the epidural drug, and a comparison of the total drug administered would compare in favor of the epidural technique.

Finally, were there any differences in preoperative injuries, such as rib fractures in one group *versus* pulmonary contusion in another? I suspect the stratification over time of these preoperative variables and preoperative injuries would show a clear advantage for the epidural technique.

Overall, this is a difficult clinical comparative study that will eventually show a clear advantage for epidural anesthesia, and I encourage the authors to continue to enroll patients until that advantage is defined in terms of outcome clinical measurements.

PRESIDENT GRIFFEN: I remind you that discussants are limited to three minutes.

DR. JAMES V. SITZMANN (Washington, D.C.): You might wonder why a GI hepatobiliary surgeon is commenting on this paper, but

I owe that to Dr. Fischer for asking me. I think (this paper) is a great example of translational research, and it reflects the ongoing clinical and basic science research at the University of Cincinnati.

My question is along the lines of the IL-8, which has been shown to relate to increased PMNs, as you heard, in the lung-injured patient. I was thinking that IL-8 changes, by some authors, have related to differences in the lung injury, and could that relate to the variability of lung injury in the two groups, as has been reflected in some of the other discussants? But, further, couldn't it just be reflective of improved pulmonary function and not necessarily causative, but rather, reflective of the improved pulmonary function in the epidural group?

Lastly, some have suggested that the degree of inflammatory response after injury relates to the balance of proinflammatory cytokines such as the ones measured in this study, IL-6, IL-8 and TNF-α in conjunction with the antiinflammatory cytokines such as IL-10. Did you consider or did you measure IL-10 levels? And do you think that would be a fruitful line of inquiry?

Lastly, several studies have shown that severity of injury relates to IL-6 levels. I was impressed with the graph that showed a marked diminution in those levels. Do you think that has a potential role as a marker for the surgeon handicapping or grading the severity of injury?

PRESIDENT GRIFFEN: I am particularly interested in why the length of stay, both in the ICU and the hospital was less in the PCA group, even though they had less successful pain management.

DR. M. RYEN MOON (Closing Discussion): In response to Dr. Pruitt, first, there was no difference in body temperature between the patients randomized into the epidural or the PCA group.

A common theme amongst all the questions asked today was, first of all, the total length of time or days spent on the ventilator with mechanical ventilation and the incidence of pneumonia. Kind of touching base on all three or four of the discussants who asked these questions, we have not as yet compiled the total numbers of patients that had complications such as pneumonia or bronchitis. One of the problems with that is the study was looked at over a 3-day period, so I think one of the next projects to do is to follow those patients after that 3-day period.

As far as the use of anti–IL-8 agents or receptor antagonists, I think that is a very good point, and we currently have several ongoing studies dealing specifically with acute lung injury, a lot of nitric oxide studies, and I think it's in the works in the future.

In response to Dr. Carrico's questions about the immune response, I think you are absolutely right in saying that. Probably a better phrase for that was a modification, a stronger statement. However, with the association of IL-8 and its potential relationship to PMN and neutrophil attractant and infectious complications, I think it favors that.

The question concerning difference in infection between two groups: as I stated earlier, I think part of the problem was this study looked at a very short period of time over 3 days. And if you were to possibly enroll more patients over the next 1 or 2 years and extend this out and look at patients past the 3-day period, we may be able to tease that out. But we did not look at that or compile that number yet.

Complications within the two groups: there was one patient that was randomized to the epidural group that had to be removed because of persistent hypotension. Similarly, there was one patient that was randomized to the PCA group that was excluded because her husband was clicking the PCA button for her. So that was a rather interesting withdrawal. She almost went into full respiratory distress.

Remarkably, though, over the 24 total enrolled and the 13 patients enrolled in the epidural group, there weren't any catheter malpositions or malfunctions. Our biggest concern initially was the hypotension, but that was closely followed by the pain service, and they dictated the pain control for both groups.

Drug levels for both groups. I think we were using as an end point patient—it's a very subjective way of reasoning—patient comfort in this study. So I assume that the drug levels in both groups, if you looked at the epidural and the PCA group, you'd see a wide variation.

As you know, one patient with multiple rib fractures may have a higher pain threshold compared to another patient and therefore, their use of the PCA or requirements of pain medication may be higher. But using the patient comfort as an end point, I think there is no way we could control for that.

There was no significant difference in terms of rib fractures or pulmonary contusions between both groups. They were very well matched. One explanation for difference in length of stay between the two groups, although there was no statistically significant difference, could be the systemic absorption of the opioids, causing a postinjury ileus. We have to invest more time into looking at, as I mentioned earlier, complication rates.

Dr. Sitzmann's question regarding IL-10: no, we did not look at levels of IL-10, and that's actually a very interesting point. In the future we possibly can look at levels of IL-10.

PRESIDENT GRIFFEN: I don't know who was clicking your buttons on the PCA, but if your patient went into respiratory distress, somebody doesn't know how to use the equipment.